FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 14:56:03 ON 07 JUL 2004

		E	PILARSKI LINDA/IN,AU
L1	152	S	E1-9
L2	71901	S	HYALURON?
L3	28	S	L1 AND L2
L4	132308	S	DENDRITIC
L5	167187	S	HEMATOPOIETIC
L6	1925996	S	CANCER
L7	263650	S	ANEMIA
L8	202237	S	STEM CELL
L9	79005	S	IMMUNOMOD?
L10	862891	S	TRANSPLANT?
L11	19		DUP REM L3 (9 DUPLICATES REMOVED)
L12	19	S	L11 AND (L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L2

L12 ANSWER 1 OF 19 MEDLINE on STN
ACCESSION NUMBER: 2003281238 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12808028
TITLE: RHAMM is a centrosomal protein that interacts with dynein and maintains spindle pole stability.
AUTHOR: Maxwell Christopher A; Keats Jonathan J; Crainie Mary; Sun Xuejun; Yen Tim; Shibuya Ellen; Hendzel Michael; Chan Gordon; **Pilarski Linda M**
CORPORATE SOURCE: Department of Oncology, University of Alberta/Cross Cancer Institute, Edmonton Alberta Canada T6G 1Z2.
CONTRACT NUMBER: CA06927 (NCI)
GM-44762 (NIGMS)
P01 CA75138 (NCI)
SOURCE: Molecular biology of the cell, (2003 Jun) 14 (6) 2262-76. Journal code: 9201390. ISSN: 1059-1524.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20030617
Last Updated on STN: 20040221
Entered Medline: 20040220

AB The receptor for **hyaluronan**-mediated motility (RHAMM), an acidic coiled coil protein, has previously been characterized as a cell surface receptor for **hyaluronan**, and a microtubule-associated intracellular **hyaluronan** binding protein. In this study, we demonstrate that a subset of cellular RHAMM localizes to the centrosome and functions in the maintenance of spindle integrity. We confirm a previous study showing that the amino terminus of RHAMM interacts with microtubules and further demonstrate that a separate carboxy-terminal domain is required for centrosomal targeting. This motif overlaps the defined **hyaluronan** binding domain and bears 72% identity to the dynein interaction domain of Xklp2. RHAMM antibodies coimmunprecipitate dynein IC from Xenopus and HeLa extracts. Deregulation of RHAMM expression inhibits mitotic progression and affects spindle architecture. Structure, localization, and function, along with phylogenetic analysis, suggests that RHAMM may be a new member of the TACC family. Thus, we demonstrate a novel centrosomal localization and mitotic spindle-stabilizing function for RHAMM. Moreover, we provide a potential mechanism for this function in that RHAMM may cross-link centrosomal microtubules, through a direct interaction with microtubules and an association with dynein.

L12 ANSWER 2 OF 19 MEDLINE on STN
ACCESSION NUMBER: 2003200152 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12720129
TITLE: Abnormal expression of **hyaluronan** synthases in patients with Waldenstrom's macroglobulimenia.
AUTHOR: Adamia Sophia; Crainie Mary; Kriangkum Jitra; Mant Michael J; Belch Andrew R; **Pilarski Linda M**
CORPORATE SOURCE: Department of Oncology, University of Alberta and Cross Cancer Institute, Edmonton, Alberta, Canada.
SOURCE: Seminars in oncology, (2003 Apr) 30 (2) 165-8. Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030430
Last Updated on STN: 20030603
Entered Medline: 20030602

AB Little is known about the biology or spread of Waldenstrom's macroglobulinemia (WM), a lymphoplasmo-proliferative disorder. **Hyaluronan** synthases (HASs), plasma membrane proteins, synthesize the extracellular matrix molecule **hyaluronan** (HA), which plays a role in malignant cell migration and the spread of many **cancers**. Three isoenzymes of HAS-HAS1, HAS2, and HAS3-are detected in humans. Aberrant expression of the HASs is coupled with different abnormalities. We have analyzed the expression pattern of HASs in WM patients. HAS3 was expressed in all patients and healthy donors tested, whereas the expression of HAS1 and HAS2 varied among the WM patients. Additionally, in WM patients, we have detected novel variants of HAS1, one of which was also detected in multiple myeloma (MM) patients. We speculate that HAS1 variants synthesize the intracellular HA ligand for RHAMM (a receptor for HA). RHAMM contributes to genetic instability in MM; therefore, we

speculate that it may also contribute to genetic instability in WM. Furthermore, we suggest that overexpression of HAS1 and its variants in combination with HAS3 may form an HA matrix around WM cells, thus preventing their elimination by the immune system, and it promotes their migration and may facilitate the spread of disease.

L12 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2004:184556 BIOSIS
DOCUMENT NUMBER: PREV200400181654
TITLE: Aberrant splicing of **hyaluronan** synthase 1 (HAS1) gene in multiple myeloma (MM): HAS1 and novel HAS1 splice variants in MM B cells have an adverse impact on patient survival.
AUTHOR(S): Adamia, Sophia [Reprint Author]; Reiman, Tony [Reprint Author]; Crainie, Mary [Reprint Author]; Belch, Andrew R. [Reprint Author]; **Pilarski, Linda M.** [Reprint Author]
CORPORATE SOURCE: Oncology, University of Alberta and Cross Cancer Institute, Edmonton, AB, Canada
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 371b. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Apr 2004
Last Updated on STN: 7 Apr 2004

AB **Hyaluronan** (HA) is synthesized by the family of three HAS genes. Previously, we have identified the cell-type specific expression of these genes in MM B and plasma cells (PC). MM B cells express the HAS1 while MM PCs are characterized by the expression of HAS2. HAS3 transcripts are ubiquitously expressed in all analyzed MM patients including healthy donors. HAS1 and HAS2 are undetectable in healthy donors. We have identified three abnormal novel splice variants of HAS1 gene, HAS1Va, HAS1Vb and HAS1Vc, in circulating MM B cells. Cloning, sequencing, and alignment analysis of HAS1 gene PCR products amplified from three MM patients show that HAS1Va lacks exon 4 and has a point mutation in an upstream exon. HAS1Vb has a partial retention of intron 4 coupled with deletion of exon 4. HAS1Vc retains exon 4 and includes intron 4. This very rare intronic splicing appears to be a characteristic of a cell with malignant phenotype and may cause a -1 ribosomal frameshift. All three aberrantly spliced transcripts are predicted to encode severely truncated HAS1 variant proteins that maintain the HA synthetic domains but are unable to fold correctly in the membrane and translocate HA chain into the extracellular matrix. Since in many **cancers** splicing signals are frequent targets of mutations, we initiated screening of MM patients to identify the point mutation which appears to be characteristic of HAS1Va. Based on sequence and alignment analysis we speculate that this point mutation which is located on the highly conserved exon of HAS1, promotes activation of cryptic splice sites and consequently mediates aberrant splicing of HAS1 gene. Occurrence of the point mutation in HAS1Va transcripts suggests the presence of a new variant allele of HAS1 in MM patients which may be a novel disease marker. This point mutation does not hinder HA synthesis, and may mediate accumulations of intracellular HA. HA is a ligand for both surface and intracellular RHAMM. Inside the cell, RHAMM is a centrosomal protein likely mediating genetic instability in MM. Thus, HAS1 and its novel variants not only promote RHAMM-dependent MM B cell migration, as previously demonstrated by us, but through synergy with RHAMM, may promote the emergence of increasingly aggressive genetic variants in MM. The statistical analysis of 41 MM PBMC showed that expression of HAS1 and its novel splice variants correlate strongly with poor survival in these patients (HAS1 P=0.03, HAS1Va P=0.03, and HAS1Vb P=0.002). Longitudinal analysis of HAS1 and its novel variants in 26 MM patients indicates that the majority of the patients express HAS1 and its novel variants at diagnosis and as they relapse. HAS1Vb is first survival marker to be described that reflects properties of circulating, malignant MM B cells. This provides evidence in support of a key role for early stage MM cells, and highlights potential mechanisms through which MM B cells may impact disease progression. Their correlation with reduced patient survival supports the idea that HAS1 and the highly abnormal HAS1 splice variants are central components of disease progression in MM.

L12 ANSWER 4 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2004:152373 BIOSIS
DOCUMENT NUMBER: PREV200400147849
TITLE: Microsystems and **cancer**: Improved detection of disease related genes in myeloma patients using microfluidics platforms.
AUTHOR(S): Adamia, Sophia [Reprint Author]; Pilarski, Patrick M. [Reprint Author]; Prakash, Ranjit; Lauzon, Jana [Reprint Author]; Backhouse, Chris J.; **Pilarski, Linda M.** [Reprint Author]
CORPORATE SOURCE: Oncology, Ctoss Cancer Institute, Edmonton, AB, Canada
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 682a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB Understanding the risk factors for developing any type of **cancer**, including Multiple Myeloma (MM), will provide insight into strategies that may increase the length and quality of life for afflicted individuals. Identification of the genetic signature for each **cancer** is likely to enable predictions of risk and stratification of treatment. The capabilities of PCR and RT-PCR have accelerated progress in the measurement of molecular and genetic changes in patients, thus increasing identification of the genetic signatures of many types of **cancers**. The products obtained from PCR are measured by gel-based analysis that frequently fails to detect low-level expressed genes or genes with shorter lifespan. Capillary electrophoresis (CE), a more sensitive method, offers successful detection of low-level expressed genes. However, this method is time-consuming, expensive, and cannot be performed in routine clinical testing. Integrated and automated microfluidic chips (MFCs) offer an alternative means to measure molecular and genetic changes in patients when using, for example, diagnostic/monitoring tests such as PCR, CE, and fluorescent staining. These can be rapidly performed using minute amounts of tissue without specialized operators. Automated MFCs offer many advantages over existing macroscale systems: compactness, disposability, reproducibility, and decreased sample volumes. We are using MFCs to develop novel microsystems for fast, accurate and real time genetic screening of MM patients. Comparative analysis confirms analysis of PCR products on-chip is as sensitive, sometimes considerably more so, than conventional analysis of PCR products using capillary electrophoresis. On-chip PCR is robust and less susceptible to contamination than is conventional electrophoresis. On-chip sample processing, and the ability to detect product with few cycles of PCR, indicates that quantitative PCR is feasible. We tested the practical aspects and limitations of a microfluidics approach by amplifying **hyaluronan** synthase 1 (HAS1) and its novel splice variants in MM patients and in cell lines. HAS1 and its novel variants appear to be the first described markers of circulating MM B cells with clinical predictive value, whose expression correlates with poor survival. They belong to a group of short-lived genes that are difficult to amplify by conventional gel-based analysis. On-chip analysis enabled detection of HAS1 and its novel variants PCR products after 15 cycles of PCR. The same product is undetectable with CE even when concentrating 25ul of PCR reaction. We successfully performed on-chip PCR using an automated valving system and amplified HAS1 and its novel splice variants in 2ul of total PCR reaction. This work forecasts high-throughput automated devices able to analyze genetic information using minimal amounts of genetic material in minutes, inexpensively. Once fully integrated systems capable of seamless sample processing, selecting cells of interest and performing genetic analyses of individual cells or groups of cells are available for clinical use, we anticipate that they will contribute significantly at the time of diagnosis and facilitate monitoring genetic characteristics of the malignant clone at every subsequent clinic visit. Real time detection of complex genetic abnormalities in a given **cancer** clone is likely to detect aggressive variants as they arise and thus enable the development of therapeutic options tailored to the genetic signature of a **cancer** in each individual patient, at diagnosis and as **cancer** progresses.

L12 ANSWER 5 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:367781 BIOSIS
DOCUMENT NUMBER: PREV200300367781

TITLE: **Hyaluronan** Synthases May Potentiate Waldenstrom's Macroglobulinemia.

AUTHOR(S): Adamia, Sophia [Reprint Author]; Kriangkum, Jitra [Reprint Author]; Crainie, Mary [Reprint Author]; Belch, Andrew R. [Reprint Author]; Mant, Michael J. [Reprint Author]; **Pilarski, Linda M.** [Reprint Author]

CORPORATE SOURCE: Oncology, Cross Cancer Institute/University of Alberta, Edmonton, AB, Canada

SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 4297. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 13 Aug 2003
Last Updated on STN: 13 Aug 2003

AB Waldenstrom's macroglobulinemia (WM), a lymphoplasmo-proliferative disorder, shares clinical and pathological similarities with multiple myeloma (MM). WM is characterized by the presence of monoclonal IgM in the serum of patients and bone marrow (BM) infiltration by lymphocytes, plasmacytoid cells and plasma cells. **Hyaluronan** (HA), a major extracellular matrix (ECM) molecule, plays a significant role in malignant cell migration and the spread of many **cancers** including MM. This simple, multifunctional carbohydrate is synthesized by **hyaluronan** synthases (HASs), which are a family of trans-membrane proteins. HASs perform 6 different functions to produce and translocate HA molecules into the ECM. In addition to extracellular HA, an intracellular and nuclear HA has been identified. Intracellular HA may associate with cell signaling molecules while nuclear HA is suggested to be involved in chromatin condensation and mitosis. Three evolutionarily conserved isoenzymes of HAS-HAS1, HAS2, and HAS3-have been detected in humans. Each HAS isoenzyme is characterized by distinct enzymatic activities, producing a different sizes of HA with different cell- and tissue-specific functions. Using the DNA fragment analysis approach, we have analyzed the expression pattern of HAS genes in BM aspirates (n=10) and in the peripheral blood (PB) of patients (n=8) with WM. The HAS3 gene was expressed in all samples and 10 previously analyzed healthy donors. Unlike MM patients the expression pattern of HAS1 and HAS2 varied among individual WM patients. HAS1 transcripts were detected in the BM of 9/10 patients and the PB of 4/8 patients. HAS2 was expressed in 6/8 PB samples and 6/10 BM aspirates from patients with WM. Our observations to date suggest the existence of a heterogeneous population of malignant cells in the tested WM patients as well as a degree of patient specificity. Additionally, in all tested WM patients, we have detected one and sometimes two novel variants of HAS1-HAS1V (a) and HAS1V (b), the latter of which is unique to WM. HAS1V(a) transcripts were expressed 6/10 BM and 5/8 PB samples, while HAS1V (b) was expressed 1/10 BM and 3/8 PB samples. Novel HAS-1 variants were not detected in healthy donors. We speculate that HAS1 variants synthesize the intracellular HA ligand for RHAMM (Receptor for HA Mediated Motility). Since RHAMM contributes to genetic instability in myeloma, we speculate that it may also contribute to genetic instability in WM. Based on our preliminary results, we suggest that overexpression of full-length HAS1 and HAS2 may form an extracellular HA matrix around WM cells, thus preventing their elimination by the immune system, while intracellular HA alters cell signaling and/or mitosis. In addition, the existence of an HA matrix around the malignant cells is likely to promote their migration and, consequently, may facilitate the spread of disease. HAS2, HAs1 and the HAS1 splice variants are strongly overexpressed and may potentiate the malignant process in WM. Thus, HASs may contribute to genetic instability and malignant spread in WM.

L12 ANSWER 6 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2002:186712 BIOSIS

DOCUMENT NUMBER: PREV200200186712

TITLE: **Hyaluronan** synthases as potential oncogenes in myeloma.

AUTHOR(S): Adamia, Sophia [Reprint author]; Crainie, Mary [Reprint author]; Belch, Andrew R. [Reprint author]; **Pilarski, Linda M.** [Reprint author]

CORPORATE SOURCE: Oncology, University of Alberta/Cross Cancer Institute, Edmonton, AB, Canada

SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 373a. print.
Meeting Info.: 43rd Annual Meeting of the American Society

of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Mar 2002
Last Updated on STN: 13 Mar 2002

AB Previous molecular studies revealed existence of circulating B cells in the peripheral blood of patients with multiple myeloma (MM). These drug-resistant clonotypic cells express the RHAMM oncogene and require **hyaluronan** (HA) for their motility. The overexpression and/or inhibition of intracellular RHAMM dysregulates mitosis, likely leading to chromosomal instabilities, while surface RHAMM contributes to malignant spread by mediating HA-dependent motility. As a ligand for RHAMM, HA may have a profound impact on MM progression through synergy between RHAMM and **hyaluronan** synthases (HASs). HASs are membrane proteins which synthesise and translocate HA molecules to the cell exterior. Three isozymes of HAS - HAS1, HAS2, and HAS3 have been detected in humans, each of which produces a different size range of HA polymers. Using RT-PCR capillary electrophoresis (GeneScan Analysis) we examined the expression pattern of HAS isozymes in B and plasma cells from 7 patients with MM and 4 MGUS patients, as compared to HAS expression in B cells from 4 normal donors. HAS3 is expressed ubiquitously in all the tested patients and normal donors. However, HAS1 and HAS2 exhibit cell-type specific expression B and plasma cells respectively. Overexpressed HAS-1 was detectable at diagnosis and after treatment of MM patients. MM B cells, which overexpress HAS1, synthesize extracellular HA halos, as confirmed by use of a particle exclusion assay combined with indirect HA staining. No HA halos were detectable for MM plasma cells nor for normal B cells. This suggests that HAS1 may be an important component of spread since only MM B cells have migratory capability. GeneScan analysis also revealed novel variant of HAS1, HAS1V, that is greatly overexpressed in malignant B cells but undetectable in plasma cells, normal B cells or T cells from normal and MM donors. Although undetectable in control CCL-110 fibroblasts by conventional gel analysis or Genescan, we have detected small amounts of HAS-1V transcripts in PCR products concentrated by precipitation, suggesting that it may be a normal gene product that is greatly overexpressed in MM B cells. B cells from a subset of untreated patients with MM and MGUS expressed exclusively HAS1V with no detectable HAS1. The extensive overexpression of HAS1V in 2/4 MGUS patients suggests that its overexpression may be an early event in myelomagenesis. HAS1V appears to be an intracellular isozyme which may synthesize intracellular HA, a ligand for intracellular RHAMM, and thus contribute to the RHAMM-induced dysregulation of mitosis and subsequent chromosomal abnormalities. The pattern of HAS1 isozyme expression parallels that of RHAMM, with distinct effects of surface-localized HAS1 which potentiates malignant spread, and intracellular HAS1V which may contribute to the extensive genetic instability that characterizes multiple myeloma. We speculate that overexpression of HAS1 and its novel variant HAS1V is an early event in the tranformation from MGUS to MM, and that HAS1 isozymes contribute to the progression of myeloma through synergy with the RHAMM oncogene.

L12 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:177746 BIOSIS
DOCUMENT NUMBER: PREV200200177746
TITLE: RHAMM and the centrosome: Uncovering a relationship with the kinesin-like protein2 (Klp2) and transforming acidic coiled coil protein (TACC) families.
AUTHOR(S): Maxwell, Christopher A. [Reprint author]; Keats, Jonathan J.; Crainie, Mary; **Pilarski, Linda M.**
CORPORATE SOURCE: Experimental Oncology, Cross Cancer Institute, 11560 University Ave, Edmonton, AB, T6G 1Z2, Canada
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 242a. print.
Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology. Washington DC, USA. December 08-12, 2001. American Society for Cell Biology.
CODEN: MBCEEV. ISSN: 1059-1524.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 2002
Last Updated on STN: 6 Mar 2002

L12 ANSWER 8 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:154535 BIOSIS

DOCUMENT NUMBER: PREV200200154535
TITLE: Affinity of RHAMM isoforms for interphase and mitotic microtubules in suspension cells.
AUTHOR(S): Maxwell, Christopher A. [Reprint author]; **Pilarski, Linda M.**
CORPORATE SOURCE: Experimental Oncology, Cross Cancer Institute, 11560 University Ave, Edmonton, AB, T6G 1Z2, Canada
SOURCE: Molecular Biology of the Cell, (Dec., 2000) Vol. 11, No. Supplement, pp. 200a-201a. print.
Meeting Info.: 40th American Society for Cell Biology Annual Meeting. San Francisco, CA, USA. December 09-13, 2000. American Society for Cell Biology.
CODEN: MBCEEV. ISSN: 1059-1524.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2002
Last Updated on STN: 26 Feb 2002

L12 ANSWER 9 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:234379 BIOSIS
DOCUMENT NUMBER: PREV199900234379
TITLE: Potential role for **hyaluronan** and the **hyaluronan** receptor RHAMM in mobilization and trafficking of **hematopoietic** progenitor cells.
AUTHOR(S): **Pilarski, Linda M.** [Reprint author]; Pruski, Eva; Wizniak, Juanita; Paine, Darlene; Seeberger, Karen; Mant, Michael J.; Brown, Christopher B.; Belch, Andrew R.
CORPORATE SOURCE: Cross Cancer Institute, 11560 University Ave, Edmonton, AB, T6G1Z2, Canada
SOURCE: Blood, (May 1, 1999) Vol. 93, No. 9, pp. 2918-2927. print.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Jun 1999
Last Updated on STN: 17 Jun 1999

AB Although the mechanism(s) underlying mobilization of **hematopoietic** progenitor cells (HPCs) is unknown, detachment from the bone marrow (BM) microenvironment and motility are likely to play a role. This work analyzes the motile behavior of HPCs and the receptors involved. CD34+45lo/medScatterlo/med HPCs from granulocyte colony-stimulating factor (G-CSF)-mobilized blood and mobilized BM were compared with steady-state BM for their ability to bind **hyaluronan** (HA), their expression of the HA receptors RHAMM and CD44, and their motogenic behavior. Although RHAMM and CD44 are expressed by mobilized blood HPCs, function blocking monoclonal antibodies (MoAbs) identified RHAMM as a major HA binding receptor, with a less consistent participation by CD44. Permeabilization of mobilized blood HPCs showed a pool of intracellular (ic) RHAMM and a smaller pool of icCD44. In contrast, steady-state BM HPCs have significantly larger pools of icRHAMM and icCD44. Also, in contrast to mobilized blood HPCs, for steady-state BM HPCs, MoAbs to RHAMM and CD44 act as agonists to upregulate HA binding. The comparison between mobilized and steady-state BM HPCs suggests that G-CSF mobilization is associated with depletion of intracellular stores of HA receptors and modulates HA receptor usage. To confirm that mobilization alters the HA receptor distribution and usage by HPCs, samples of BM were collected at the peak of G-CSF mobilization in parallel with mobilized blood samples. HA receptor distribution of mobilized BM HPCs was closely matched with mobilized blood HPCs and different from steady-state BM HPCs. Mobilized BM HPCs had lower pools of icHA receptors, similar to those of mobilized blood HPCs. Treatment of mobilized BM HPCs with anti-RHAMM MoAb decreased HA binding, in contrast to steady-state BM HPCs. Thus, G-CSF mobilization may stimulate an autocrine stimulatory loop for HPCs in which HA interacts with basal levels of RHAMM and/or CD44 to stimulate receptor recycling. Consistent with this, treatment of HPCs with azide, nystatin, or cytochalasin B increased HA binding, implicating an energy-dependent process involving lipid rafts and the cytoskeleton. Of the sorted HPCs, 66% were adherent and 27% were motile on fibronectin plus HA. HPC adherence was inhibited by MoAbs to beta1 integrin and CD44, but not to RHAMM, whereas HPC motility was inhibited by MoAb to RHAMM and beta1 integrin, but not to CD44. This finding suggests that RHAMM and CD44 play reciprocal roles in adhesion and motility by HPCs. The G-CSF-associated alterations in RHAMM distribution and the RHAMM-dependent motility of HPCs suggest a potential role for HA and RHAMM in trafficking of HPCs and the possible use of HA as a mobilizing agent in vivo.

L12 ANSWER 10 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:151484 BIOSIS

DOCUMENT NUMBER: PREV199900151484
TITLE: Overexpression of the receptor for **hyaluronan** -mediated motility (RHAMM) characterizes the malignant clone in multiple myeloma: Identification of three distinct RHAMM variants.
AUTHOR(S): Crainie, Mary; Belch, Andrew R.; Mant, Michael J.; **Pilarski, Linda M.** [Reprint author]
CORPORATE SOURCE: Dep. Oncol., Univ. Alberta, Edmonton, AB T6G 1Z2, Canada
SOURCE: Blood, (March 1, 1999) Vol. 93, No. 5, pp. 1684-1696. print.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Apr 1999
Last Updated on STN: 13 Apr 1999

AB The receptor for **hyaluronan** (HA)-mediated motility (RHAMM) controls motility by malignant cells in myeloma and is abnormally expressed on the surface of most malignant B and plasma cells in blood or bone marrow (BM) of patients with multiple myeloma (MM). RHAMM cDNA was cloned and sequenced from the malignant B and plasma cells comprising the myeloma B lineage hierarchy. Three distinct RHAMM gene products, RHAMM, RHAMM-48, and RHAMM-147, were cloned from MM B and plasma cells. RHAMM was 99% homologous to the published sequence of RHAMM. RHAMM-48 and RHAMM-147 variants align with RHAMM but are characterized by sequence deletions of 48 bp (16 amino acids (aa)) and 147 bp (49 aa), respectively. The relative frequency of these RHAMM transcripts in MM plasma cells was determined by cloning of reverse-transcriptase polymerase chain reaction (RT-PCR) products amplified from MM plasma cells. Of 115 randomly picked clones, 49% were RHAMM, 47% were RHAMM-48, and 4% were RHAMM-147. All of the detected RHAMM variants contain exon 4, which is alternatively spliced in murine RHAMM, and had only a single copy of the axon 8 repeat sequence detected in murine RHAMM. RT-PCR analysis of sorted blood or BM cells from 22 MM patients showed that overexpression of RHAMM variants is characteristic of MM B cells and BM plasma cells in all patients tested. RHAMM also appeared to be overexpressed in B lymphoma and B-chronic lymphocytic leukemia (CLL) cells. In B cells from normal donors, RHAMM was only weakly detectable in resting B cells from five of eight normal donors or in chronically activated B cells from three patients with Crohn's disease. RHAMM-48 was detectable in B cells from one of eight normal donors, but was undetectable in B cells of three donors with Crohn's disease. RHAMM-147 was undetectable in normal and Crohn's disease B cells. In situ RT-PCR was used to determine the number of individual cells with aggregate RHAMM transcripts. For six patients, 29% of BM plasma cells and 12% of MM B cells had detectable RHAMM transcripts, while for five normal donors, only 1.2% of B cells expressed RHAMM transcripts. This work suggests that RHAMM, RHAMM-48, and RHAMM-147 splice variants are overexpressed in MM and other B lymphocyte malignancies relative to resting or in vivo-activated B cells, raising the possibility that RHAMM and its variants may contribute to the malignant process in B-cell malignancies such as lymphoma, CLL, and MM.

L12 ANSWER 11 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:97926 BIOSIS
DOCUMENT NUMBER: PREV199900097926
TITLE: Overexpression of the **hyaluronan** receptor RHAMM characterizes the malignant clone in multiple myeloma: Identification of three distinct RHAMM variants.
AUTHOR(S): **Pilarski, Linda M.** [Reprint author]; Crainie, Mary; Mant, Michael J.; Belch, Andrew R.
CORPORATE SOURCE: Dep. Oncol. and Med., Univ. Alberta, Edmonton, AB, Canada
SOURCE: Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 257A. print.
Meeting Info.: 40th Annual Meeting of the American Society of Hematology. Miami Beach, Florida, USA. December 4-8, 1998. The American Society of Heamatology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Mar 1999
Last Updated on STN: 4 Mar 1999

L12 ANSWER 12 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:49086 BIOSIS
DOCUMENT NUMBER: PREV199900049086
TITLE: During human thymic development, beta1 integrins regulate adhesion, motility, and the outcome of RHAMM/

hyaluronan engagement.
AUTHOR(S): Gares, Sheryl L. [Reprint author]; Giannakopoulos, Nadia; Macneil, Donna; Faull, Randall J.; **Pilarski, Linda M.** [Reprint author]
CORPORATE SOURCE: Dep. Oncol., Univ. Alberta, Edmonton, AB T6G 1Z2, Canada
SOURCE: Journal of Leukocyte Biology, (Dec., 1998) Vol. 64, No. 6, pp. 781-790. print.
CODEN: JLBIE7. ISSN: 0741-5400.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Feb 1999
Last Updated on STN: 10 Feb 1999

AB During human thymic differentiation, interactions between fibronectin (Fn)/beta1 integrins and **hyaluronan** (HA)/RHAMM control motility and Fn/beta1 integrins mediate spontaneous Fn-dependent adhesion. Multinegative (MN, CD3-4-8-) thymocytes exhibit strong spontaneous adherence to Fn (75%) that was efficiently inhibited by anti-alpha5beta1 and only weakly inhibited by anti-alpha4beta1. The relatively weak adherence of unfractionated thymocytes to Fn required both alpha4beta1 and alpha5beta1. Video time-lapse microscopy indicates that a subset of thymocytes also undergo spontaneous Fn-dependent motility mediated by alpha5beta1, alpha4beta1, and the HA-receptor RHAMM, but not by CD44. The loss of motility after **hyaluronidase** treatment of thymocytes indicated that motility is strongly dependent on HA. Of motile cells, 55% were DP, 19% were DN, and 24% were CD4+SP, but only 1% were CD8+SP. Overall, for MN thymocytes, beta1 integrin mediated Fn-adhesion, but after expression of CD4/ CD8, beta1 integrins mediated Fn-dependent motility. Treatment with the activating anti-beta1 mAb QE.2E5 inhibited thymic motility and converted otherwise nonadherent thymocytes to an adherent state. High-avidity interactions via integrins appear to supercede the motogenicity of RHAMM and HA, suggesting that integrin avidity may regulate RHAMM. During thymic development, changes in adhesion or motility appear to be mediated by integrin avidity modulation.

L12 ANSWER 13 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:54007 BIOSIS
DOCUMENT NUMBER: PREV199799353210
TITLE: Isolation of cytokeratin 18 mRNA in RHAMM positive peripheral blood cells: Implications in migration of breast **cancer** epithelial cells and establishment of micrometastasis.
AUTHOR(S): Masellis-Smith, Anna [Reprint author]; MacDonald, Dawn M.; **Pilarski, Linda M.**; Starreveld, Adalel
CORPORATE SOURCE: Dep. Oncol., Radiation Oncol., Univ. Alberta, Edmonton, AB, Canada
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 257A. Meeting Info.: Thirty-eighth Annual Meeting of the American Society of Hematology. Orlando, Florida, USA. December 6-10, 1996.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Feb 1997
Last Updated on STN: 5 Feb 1997

L12 ANSWER 14 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:53387 BIOSIS
DOCUMENT NUMBER: PREV199799352590
TITLE: **Hyaluronan** induction of RAF kinase and MAP kinase in circulating B cells but not in bone marrow plasma cells of myeloma patients.
AUTHOR(S): Masellis-Smith, Anna; Belch, Andrew R.; Ostergaard, Hanne; **Pilarski, Linda M.**
CORPORATE SOURCE: Dep. Oncology Med. Microbiol. Immunol., Univ. Alberta, Edmonton, AB, USA
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 102A. Meeting Info.: Thirty-eighth Annual Meeting of the American Society of Hematology. Orlando, Florida, USA. December 6-10, 1996.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Feb 1997
Last Updated on STN: 5 Feb 1997

L12 ANSWER 15 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:320622 BIOSIS
DOCUMENT NUMBER: PREV199396028972
TITLE: Regulated expression of a receptor for **hyaluronan** -mediated motility on human thymocytes and T cells.
AUTHOR(S): **Pilarski, Linda A.** [Reprint author]; Miszta, Helena; Turley, Eva A.
CORPORATE SOURCE: Dep. Immunol., Univ. Alberta, Edmonton, AB Can. T6G 2h7, canada
SOURCE: Journal of Immunology, (1993) Vol. 150, No. 10, pp. 4292-4302.
CODEN: JOIMA3. ISSN: 0022-1767.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Jul 1993
Last Updated on STN: 13 Jul 1993

AB A receptor for **hyaluronan**-mediated motility (RHAMM) has been shown to promote cell locomotion. Among human T lineage lymphocytes, RHAMM is expressed only on a subset of thymocytes, being absent on mature peripheral T cells from blood, spleen, and lymph node. Among thymocytes, RHAMM is selectively expressed on a subset of CD3+ CD45RA+R0+ cells, and functions in motility as shown by the ability of anti-RHAMM to reduce the speed of thymocyte locomotion from 11 mu-m/minute to 3 mu-m/min. Although freshly isolated multi-negative (MN) thymocytes (CD3-4-8-19-) lack RHAMM, its expression is induced on day 3 of culture in a variety of conditions that support differentiation, as assessed by acquisition of CD3. When MN thymocytes are cultured on plates coated with fibronectin, expression of RHAMM is prolonged, but on uncoated surfaces, its expression is transient and lost by day 7 of culture with PHA or IL-2. Culture of MN thymocytes on thymic epithelial layers, with or without IL-2, resulted in a lack of RHAMM expression. Because in the absence of epithelial cells, RHAMM is expressed, the effect appears to be one of inhibition. Although expression of RHAMM by MN thymocytes cultured with IL-2 on uncoated surfaces is transient, addition of cyclosporin A resulted in prolonged expression. These observations are consistent with the view that cyclosporin A inactivates a RHAMM-directed inhibitory mechanism. Mature peripheral blood T cells transiently express RHAMM upon culture with PHA, PMA, or IL-2. T cells that expressed RHAMM after culture with PMA alone lacked RHAMM when stimulated by mitogenic CD2 antibodies with or without CD28 antibody, indicating inhibition of RHAMM expression. Thus expression of RHAMM is regulated by a RHAMM-directed inhibitory mechanism induced by stimulation through CD2/CD28. A similar mechanism may operate in thymocyte/epithelial cell cultures. These results suggest the inhibition of RHAMM during early, presumably sessile, thymic progenitor development, followed by its induction during developmental stages when locomotion is required. The apparently strong negative regulatory control over RHAMM expression by microenvironmental factors and by known thymic and T cell signaling molecules supports this view.

L12 ANSWER 16 OF 19 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:166265 BIOSIS
DOCUMENT NUMBER: PREV199395087315
TITLE: Expression and function of a receptor for **hyaluronan**-mediated motility on normal and malignant B lymphocytes.
AUTHOR(S): Turley, Eva A.; Belch, Andrew J.; Poppema, Sibrand; **Pilarski, Linda M.** [Reprint author]
CORPORATE SOURCE: Dep. Immunology, Univ. Alberta, 845 E. Medical Science Bldg., Edmonton, Alberta T6G 2H7, Canada
SOURCE: Blood, (1993) Vol. 81, No. 2, pp. 446-453.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Mar 1993
Last Updated on STN: 1 Apr 1993

AB Migration through extracellular matrix is fundamental to malignant invasion. A receptor for **hyaluronan**-mediated motility (RHAMM) has previously been shown to play a fundamental role in locomotion of ras-transformed cells as well as functioning in signal transduction. Expression of RHAMM was characterized on B lymphocytes from normal and malignant lymphoid tissues using multiparameter phenotypic immunofluorescence analysis as well as functional analysis of its role in locomotion of malignant hairy cell leukemia B cells. RHAMM is not detectable on most normal B cells located in blood, spleen, or lymph node, but it is detectable on bone marrow and thymic B cells. Among B-cell malignancies, it is expressed on most terminally differentiated B cells from multiple myeloma bone marrows, is present on a subset of

non-Hodgkin's lymphomas, and is absent on B chronic lymphocytic leukemia. Activation of peripheral blood B cells by Staphylococcus A cowan (SAC), but not by pokeweed mitogen, induced transient expression of RHAMM at day 3 of culture, suggesting RHAMM may be used by antigen-activated normal B cells. For malignant cells, expression of RHAMM increased on long-term culture of bone marrow plasma cells from multiple myeloma patients, indicating prolonged expression in contrast to the transient expression on SAC-activated normal B cells. Intriguingly, RHAMM was expressed on hairy leukemia cells located in spleen but absent from those in peripheral blood of the same patient. RHAMM, as expressed on splenic hairy cells, was a 58-Kd molecule that binds **hyaluronan**, is encoded by a 5.2-kb messenger RNA, and participates in locomotion by these cells. Hairy cells locomoted in response to **hyaluronan** at 4 mu per minute. Monoclonal antibody to RHAMM inhibited this locomotion almost completely as detected using video time-lapse cinemicrography. These observations are consistent with a role for RHAMM in malignant invasion and metastatic growth.

L12 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:868423 CAPLUS
DOCUMENT NUMBER: 135:4435
TITLE: Balancing thymocyte adhesion and motility: A functional linkage between β1 integrins and the motility receptor RHAMM
AUTHOR(S): Gares, Sheryl L.; **Pilarski, Linda M.**
CORPORATE SOURCE: Department of Oncology, University of Alberta and Cross Cancer Institute, Edmonton, AB, T6G 1Z2, Can.
SOURCE: Developmental Immunology (2000), 7(2-4), 209-225
CODEN: DEIME7; ISSN: 1044-6672
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thymocyte differentiation involves several processes that occur in different anat. sites within the thymus. Therefore, thymocytes must have the ability to respond to signals received from stromal cells and adopt either adhesive or motile behavior. We will discuss our data indicating human thymocytes use α4β1 integrin, α5β1 integrin and RHAMM to mediate these activities. Immature multineg. (MN; CD3-4-8-19-) thymocytes use α4β1 and α5β1 integrins to mediate weak and strong adhesion. This subset also uses α4β1 integrins to mediate motility. As thymocytes differentiate, they begin to express and use RHAMM to mediate motility in conjunction with α4β1 and α5β1 integrins. Motile thymocytes use β1 integrins to maintain weakly adhesive contacts with substrate to provide traction for locomoting cells, thus weak adhesion is a requirement of motile behavior. **Hyaluronan** (HA) is also required by thymocytes to mediate motility. HA binding to cell surface RHAMM redistributes intracellular RHAMM to the cell surface where it functions to mediate motility. We propose that the decision to maintain adhesive or motile behavior is based on the balance between low and high avidity binding conformations of β1 integrins on thymocytes and that RHAMM:HA interactions decrease high avidity binding conformations of integrins pushing the balance toward motile behavior.
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:384718 CAPLUS
DOCUMENT NUMBER: 131:722
TITLE: Methods for cell mobilization using in vivo treatment with **hyaluronan**, and therapeutic methods
INVENTOR(S): **Pilarski, Linda May**
PATENT ASSIGNEE(S): Hyal Pharmaceutical Corporation, Can.
SOURCE: Can. Pat. Appl., 60 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2199756	AA	19980912	CA 1997-2199756	19970312

PRIORITY APPLN. INFO.: CA 1997-2199756 19970312
AB The use of forms of **hyaluronic** acid having a mol. weight less than about 750,000 daltons, selected from **hyaluronic** acid and pharmaceutically acceptable salts thereof, is provided for the same purposes known for using recombinant GM-CSF or G-CSF. The methods of the

invention use exogenous forms of **hyaluronic** acid for mobilizing **hematopoietic** cells to the circulation, enabling various methods of treatment (**cancer** treatment, organ **transplantation**, etc.).

L12 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:623046 CAPLUS
DOCUMENT NUMBER: 127:283374
TITLE: Methods for cell mobilization using in vivo treatment with **hyaluronan** (ha)
INVENTOR(S): **Pilarski, Linda May**
PATENT ASSIGNEE(S): Hyal Pharmaceutical Corporation, Can.; Pilarski, Linda May
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9733592	A1	19970918	WO 1997-CA172	19970312
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2173272	AA	19971003	CA 1996-2173272	19960402
CA 2173272	C	20010828		
ZA 9702124	A	19970916	ZA 1997-2124	19970312
AU 9720888	A1	19971001	AU 1997-20888	19970312
EP 914133	A1	19990512	EP 1997-906061	19970312
EP 914133	B1	20030723		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 245424	E	20030815	AT 1997-906061	19970312
PT 914133	T	20031231	PT 1997-906061	19970312

PRIORITY APPLN. INFO.: US 1996-13401P P 19960314
CA 1996-2173272 A 19960402
WO 1997-CA172 W 19970312

AB The use of forms of **hyaluronic** acid having a mol. weight less than about 750,000 daltons selected from the group consisting of **hyaluronic** acid and pharmaceutically acceptable salts thereof is provided for the same purposes known for using recombinant GM-CSF or G-CSF.